Full Text AI-92-11

THE EFFECTS OF SILICONE ON THE IMMUNE RESPONSE

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

Letter of Intent Receipt Date: September 15, 1992
Application Receipt Date: November 20, 1992

PURPOSE

The Division of Allergy, Immunology and Transplantation (DAIT) of the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invite applications for studies focused on the short- and long-term effects of silicone polymers and their breakdown products on the cellular and molecular components of the immune system and its functions and how these changes might contribute to the initiation of self-reactivity and the induction of autoimmune disease.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This Request for Applications (RFA), The Effects of Silicone on the Immune Response, is related to the priority area of diabetes and chronic disabling conditions. Potential applicants may

obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-782-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by public and private, foreign and domestic, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal Government. Women and minority investigators are encouraged to apply. Foreign institutions are not eligible to apply for the First Independent Research Support and Transition (FIRST) Award.

MECHANISM OF SUPPORT

The mechanisms of support for this program will be the research project grant (R01) and the FIRST Award (R29). The regulations (CFR Title 42, Part 52 and, as applicable to State and local governments, Title 45, Part 74) and policies that govern the research grant programs of the National Institutes of Health will prevail. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period may not exceed five years. The earliest anticipated award date will be July 1, 1993.

This RFA is a one-time solicitation. Future competing continuation applications will be considered unsolicited and compete with all investigator-initiated applications and will be reviewed according to the customary NIH peer review procedures.

FUNDS AVAILABLE

Up to $650,000 total costs for the first-year and additional approved expenses for up to five years, has been committed to fund applications submitted in response to this RFA. The NIAID and the NIAMS plan to make approximately three and one awards, respectively in FY 1993, contingent on the receipt of highly meritorious applications. Funding beyond the first and subsequent years of the grant will be contingent upon satisfactory progress during the preceding years and the availability of funds.

RESEARCH OBJECTIVES

Background

Silicone-containing implants and silicone injections have been linked to the development of autoimmune-like diseases, such as scleroderma, arthritis, and dermatomyositis, in some patients. However, there are no solid scientific data to support or rule out the link between the onset of autoimmune disease and the presence of silicone in intact or leaky implants. Furthermore, very limited information is available regarding the effects of silicone administration on the development of normal immune responses and the maintenance of self-tolerance. From the available preliminary information, it appears that some silicone polymers (e.g., D4) have biological activity in vivo similar to Freund's complete adjuvant. Basic research on the effects of silicone in the immune system will be valuable in determining the safety of these devices.

Research Goals and Scope

Some examples of relevant research topics include, but are not limited to:

o Effects of short- and long-term administration of silicone on the production, structure, and function of lymphocytes

o Effects of intracellular accumulation of silicone and low molecular weight derivatives in macrophage function, including antigen processing and presentation, cytokine production, and cytotoxic activities

o Characterization of the profiles and fine specificity of autoantibodies obtained from the sera of patients developing autoimmune-like syndromes who have also received implants

o Evaluation of the effects of silicone on lymphocyte and monocyte interactions with endothelial cells and fibroblasts and the production and function of adhesion molecules

o Analysis of silicone effects on the evolution of autoimmune disease in experimental systems, with regard to disease induction, course, and immunologic parameters.

STUDY POPULATIONS

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDIES

NIH and ADAMHA policy is that applicants for NIH/ADAMHA clinical research grants and cooperative agreements are required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study; special emphasis should be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale should be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic group. In addition, gender and racial/ethnic issues must be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information must be included in the form PHS 398 in Sections 1-4 of the Research Plan and summarized in Section 5, Human Subjects. Applicants are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of U.S. racial/ethnic minority populations (i.e., Native Americans, including American Indians or Alaskan Natives, Asian/Pacific Islanders, Blacks, and Hispanics).

The rationale for studies on single minority population groups should be provided.

For the purpose of this policy, clinical research is defined as human biomedical and behavioral studies of etiology, epidemiology, prevention, diagnosis, or treatment of diseases, disorders or conditions, including but not limited to clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are excluded. However, every effort should be made to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants.

For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the relevance of research involving foreign population groups to the U.S. populations, including minorities.

If the required information is not contained within the application, the application will be returned.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study design is inadequate to answer the scientific question(s) addressed AND the justification for the selected study population is inadequate, it will be considered a scientific weakness or deficiency in the study design and will be reflected in assigning the priority score to the application.

All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

LETTER OF INTENT

Prospective applicants are asked to submit by September 15, 1992, a letter of intent that includes a descriptive title of the overall proposed research, the name and institution of the Principal Investigator, and a list of the names of key investigators and their institution(s). The letter of intent is requested in order to provide an indication of the number and scope of applications to be reviewed to allow early preparations for review. The letter of intent is not binding and does not commit the sender to submit an application, nor is it a requirement for submission of an application. The letter of intent is to be directed to:

Susana A. Serrate-Sztein, M.D.
Chief, Autoimmunity Section
Clinical Immunology Branch
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4A20
Bethesda, MD 20892
Telephone: (301) 496-7985

APPLICATION PROCEDURES

Applications are to be submitted on the research grant application form PHS 398 (rev. 9/91). For purposes of identification and processing, the box "Yes" should be marked in item 2a on the face page of the application; the RFA number and the words "The Effects of Silicone on the Immune Response" must be entered.

These application forms are available in most institutional business offices and may be obtained from the Office of Grants Inquiries, Division of Research Grants, National Institutes of Health, 5333 Westbard Avenue, Room 449, Bethesda, MD 20892, telephone (301) 496-7441.

The receipt date for applications is November 20, 1992. Applications that are not received by November 20, 1992, or that do not conform to the instructions contained in the PHS 398 (rev. 9/91) application kit, will be returned to the applicant without review.

Submit a signed, typewritten original of the application, including the Checklist, and three signed, exact, single-sided photocopies, in one package to:

Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892

In addition, mail two exact copies of the application directly to Dr. Serrate-Sztein at the address given above under LETTER OF INTENT.

The RFA label available in the application form PHS 398 must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC program director or Principal Investigator must be included with the application.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed by the Division of Research Grants (DRG) for completeness and by NIAID and NIAMS staff for responsiveness. Applications for the FIRST Award (R29) must include at least three sealed letters of reference attached to the face page of the original application. FIRST Award (R29) applications submitted without the required number of reference letters will be considered incomplete and returned without review. Those judged to be incomplete and/or non-responsive will be returned to the applicant without review.

Applications will be reviewed for scientific and technical merit by an appropriate scientific peer review group convened by the DRG, NIH.

The second level of review will be provided by the National Advisory Allergy and Infectious Diseases Council or the National Arthritis and Musculoskeletal Diseases Council in May 1993.

Applications in response to this solicitation will be reviewed by the usual NIH peer review procedures. The factors to be considered in the evaluation of scientific merit of each application will be those used in the review of unsolicited research project grant applications, including the novelty, originality, and feasibility of the approach; the training, experience, and research competence of the investigator(s); the adequacy of the experimental design; the adequacy and suitability of the facilities; the appropriateness of the requested budget to the work proposed; and the adherence, whenever appropriate, to NIH guidelines concerning adequate representation of minorities and women in clinical research.

AWARD CRITERIA

The earliest anticipated date of award is July 1, 1993. The following will be considered in making funding decisions: quality of the proposed project as determined by peer review and availability of funds.

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Susana Serrate-Sztein, M.D.
Chief, Autoimmunity Section
Clinical Immunology Branch
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4A20
Bethesda, MD 20892
Telephone: (301) 496-7985
FAX: (301) 402-2571

Dr. Michael D. Lockshin
Director, Extramural Programs
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Building 31, Room 4C32
Bethesda, MD 20892
Telephone: (301) 496-0802

Direct inquiries regarding fiscal and administrative matters to:

Mr. Jeffrey Carow
Chief, Immunology Grants Management Section
Grants Management Branch
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4B29
Bethesda, MD 20892
Telephone: (301) 496-7075

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance, No. 93.855 - Allergy, Immunology and Transplantation Research and No. 93.846 - Arhtritis and Musculoskeletal and Skin Diseases Research. Grants are awarded under the authority of the Public Health Service Act, Section 301 (42 USC 241) and administered under PHS grants policies and Federal Regulations, most specifically at 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

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